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(54) Title: PROCESS FOR REGIOSELECTIVE SUBSTITUTION OF TRIFLUOROBENZOATE OR TRIFLUOROBENZONITRILE

(57) Abstract

The invention provides a process for regioselective substitution of trifluorobenzoate/trifluorobenzonitrile to afford the difluorobenzoate/difluorobenzonitrile in good yields. The resulting difluorobenzoate/difluorobenzonitrile can again be regioselectively substituted with a second nucleophile to give monofluorobenzoate/monofluorobenzonitrile also in good yields. This process is particularly useful for forming key intermediates in the synthesis of oxytocin antagonist compounds.

TITLE OF INVENTION
PROCESS FOR REGIOSELECTIVE SUBSTITUTION OF
TRIFLUOROBENZOATE OR TRIFLUOROBENZONITRILE

5   CROSS-REFERENCE TO RELATED APPLICATIONS
Not Applicable

STATEMENT REGARDING FEDERALLY-SPONSORED R&D
Not Applicable

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REFERENCE TO MICROFICHE APPENDIX
Not Applicable

FIELD OF THE INVENTION

15   The present invention provides a process for regioselective
substitution of trifluorobenzoate and/or trifluorobenzonitrile. More
particularly, regioselective nucleophilic substitution of 2, 4, 5-trifluoro-
benzoate/trifluorobenzonitrile at the 4-position yields 2,5-difluoro-
benzoate/difluorobenzonitrile in high yields. Subsequent substitution of
20   the 2,5-difluorobenzoate/difluorobenzonitrile at the 2-position provides
5-fluorobenzoate/fluorobenzonitrile in good yields.

BACKGROUND OF THE INVENTION
          In the field of obstetrics, one of the most important
25   problems is the management of preterm labor. A significant number of
the pregnancies progressing past 20 weeks of gestation experience
premature labor and delivery, which is a leading cause of neonatal
morbidity and mortality. Despite major advances in neonatal care,
retention of the fetus *in utero* is preferred in most instances.
30   Tocolytic (uterine-relaxing) agents that are currently in use
include β2-adrenergic agonists, magnesium sulfate and ethanol.
Ritodrine, the leading β2-adrenergic agonist, causes a number of
cardiovascular and metabolic side effects in the mother, including
tachycardia, increased renin secretion, hyperglycemia (and reactive
35   hypoglycemia in the infant). Other β2-adrenergic agonists, including

- 1 -

terbutaline and albuterol have side effects similar to those of ritodrine.
Magnesium sulfate at plasma concentrations above the therapeutic range
of 4 to 8 mg/dL can cause inhibition of cardiac conduction and
neuromuscular transmission, respiratory depression and cardiac arrest,
5   thus making this agent unsuitable when renal function is impaired.
Ethanol is as effective as ritodrine in preventing premature labor, but it
does not produce a corresponding reduction in the incidence of fetal
respiratory distress that administration of ritodrine does.

            It has been proposed that an oxytocin antagonist would be
10   the ideal tocolytic agent. In the last few years, evidence has accumulated
to strongly suggest that the hormone oxytocin may be a physiological
initiator of labor in several mammalian species including humans.
Oxytocin is believed to exert this effect in part by directly contracting
the uterine myometrium and in part by enhancing the synthesis and
15   release of contractile prostaglandins from the uterine
endometrium/decidua. These prostaglandins may, in addition, be
important in the cervical ripening process. By these mechanisms, the
process of labor (term and preterm) is initiated by a heightened
sensitivity of the uterus to oxytocin, resulting in part as a result of a
20   well-documented increase in the number of oxytocin receptors in this
tissue. This "up-regulation" of oxytocin receptors and enhanced uterine
sensitivity appears to be due to trophic effects of rising plasma levels of
estrogen towards term. By blocking oxytocin, one would block both the
direct (contractile) and indirect (enhanced prostaglandin synthesis)
25   effects of oxytocin on the uterus. An oxytocin blocker, or antagonist,
would likely be more efficacious for treating preterm labor than current
regimens. In addition, since oxytocin at term has major effects only on
the uterus, such an oxytocin antagonizing compound would be expected
to have few, if any, side effects.
30   It is also believed that an oxytocin antagonist compound
would also be useful in the treatment of dysmenorrhea. This condition
is characterized by cyclic pain associated with menses during ovulatory
cycles. The pain is thought to result from uterine contractions and
ischemia, probably mediated by the effect of prostaglandins produced in

the secretory endometrium. By blocking both the direct and indirect effects of oxytocin on the uterus, a selective oxytocin antagonist can be more efficacious for treating dysmenorrhea than current regimens. An additional use for oxytocin antagonists is for stopping labor prior to

5   cesarean delivery.

A number of potent, nonpeptide benzoxazinone oxytocin antagonists have recently been identified (see PCT International Application Publication No. WO95/02405, published January 26, 1995). Related compounds in the benzoxazinone series of oxytocin antagonists

10   which are fluorinated on the central aromatic ring, for example Compound A shown below, are also potent oxytocin antagonists.
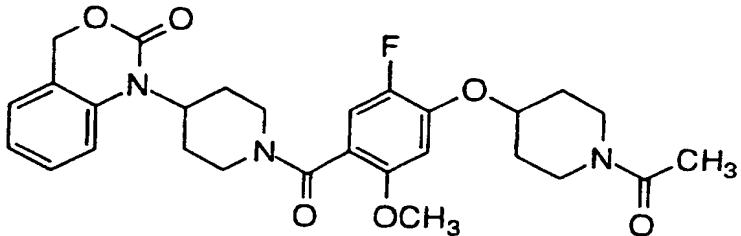
Compound A

A key intermediate in the synthesis of Compound A, and other fluorine containing structurally related oxytocin antagonist compounds, is the

15   compound 5

5
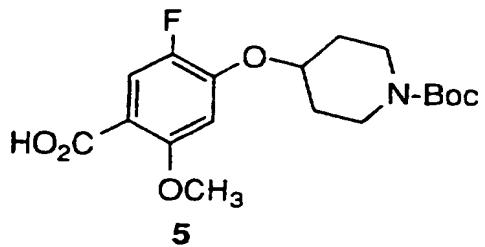
In the past, synthesis of intermediate 5 was accomplished by the direct fluorination of methyl-2,4-dihydroxylbenzoate or its analogs with N-fluoro-3,5-dichloropyridinium triflate which produced the desired 5-

20   fluorobenzoate in low yields (ca. 30%), along with the undesired 3-fluorobenzoate. *See* Schemes 1 and 2 below.

- 3 -
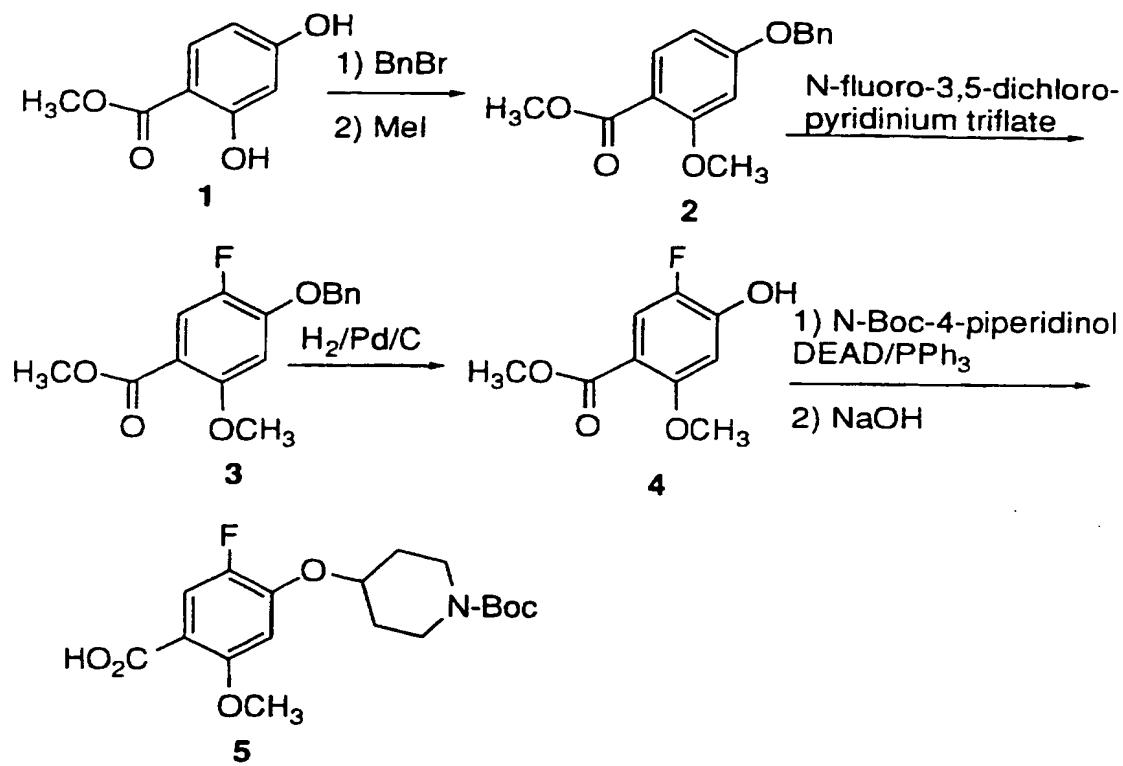
SCHEME 1

SCHEME 2
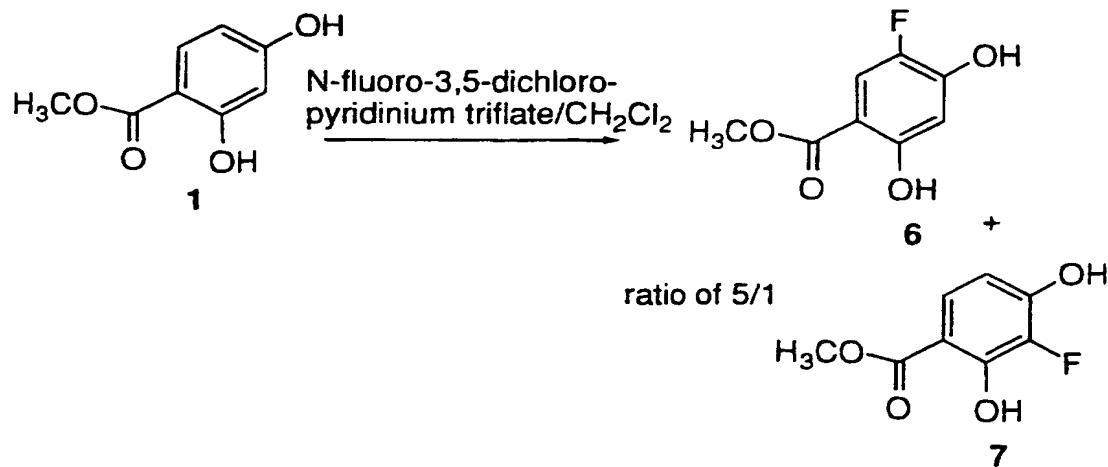
Flash chromatography was then necessary in order to remove the undesired 3-fluorobenzoate. In addition, the supply of N-fluoro-3,5-dichloropyridinium triflate is limited, and therefore, very expensive. Thus, a need remains for a more efficient synthesis of key intermediate 5 5.

It has now been found that regioselective nucleophilic substitution of trifluorobenzonitrile/trifluorobenzoate provides a more efficient and less expensive route to the desired intermediate 5 in the synthesis of oxytocin antagonists useful for preterm labor,
10 dysmenorrhea and stopping labor prior to cesarean delivery.

SUMMARY OF THE INVENTION

The present invention provides a process for forming a difluoro compound I

15
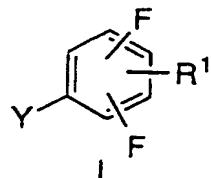
comprising reacting a trifluoro compound II
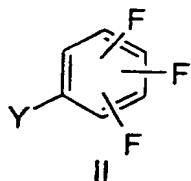
with a nucleophilic agent R^1 to obtain the difluoro compound I
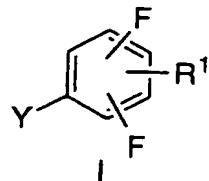
20   wherein Y is selected from CN or CO_2-C_{1-6} alkyl;
R^1 is selected from OR^3, SR^3, CN, $C \equiv CR^4$,

-5-

or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms;

R^3 is selected from C_{1-10} alkyl, C_{3-8} cycloalkyl, phenyl-C_{1-6} alkyl, phenyl or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms wherein the nitrogen containing heterocyclic ring is either unsubstituted or substituted with R^5 and R^6;

R^4 is C_{1-10} alkyl; and

R^5 and R^6 are each independently selected from CO_2R^4, COR^4 or C_{1-10} alkyl.

In one embodiment of the present invention is the process wherein the trifluoro compound is selected from
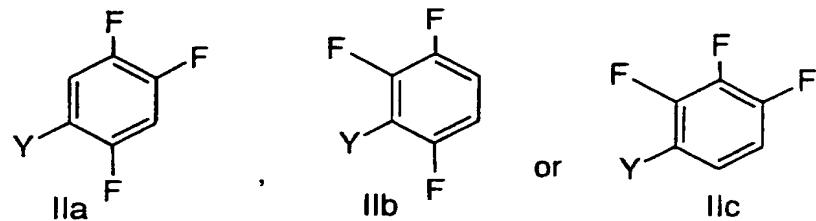
and the difluoro compound is selected from
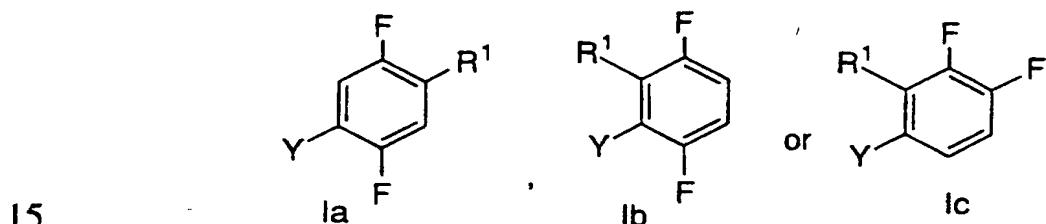
wherein all variables are as described above.

In a class of the invention is the process wherein the trifluoro compound is
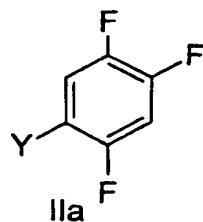
- 6 -

and the difluoro compound is

$$\text{Ia}$$
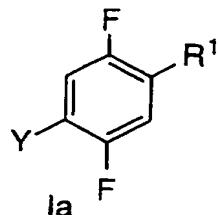
wherein all variables are as described above.

In a subclass of the invention is the process further
comprising the step of reacting the difluoro compound selected from
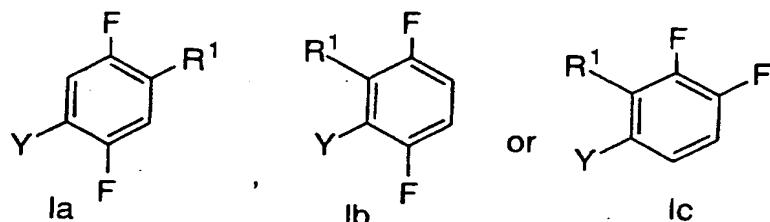
Ia   ,   Ib   or   Ic

with a second nucleophilic agent R^2 to obtain a monofluoro compound
selected from

IIIa   ,   IIIb   or   IIIc
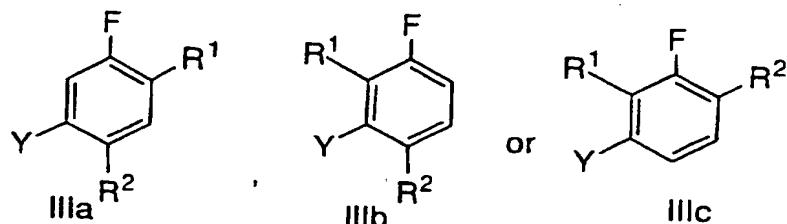
wherein R^2 is selected from OR^3, SR^3, CN, $C \equiv CR^4$,
or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic
ring containing one or two nitrogen atoms; and where all other
variables are as defined above.

Illustrative of the invention is the process wherein the difluoro compound is

Ia

and the monofluoro compound is

IIIa
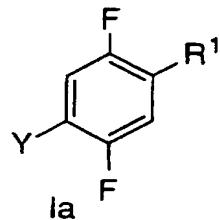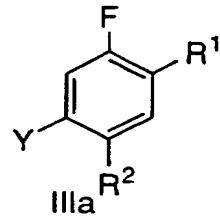
5

and where all variables are as described above.

Another aspect of the invention is a compound of the formula

     or
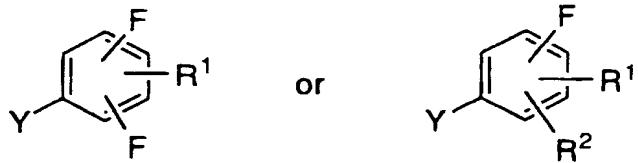
10   wherein Y is selected from CN, CO_2H or CO_2-C_{1-6} alkyl;
R^1 and R^2 are each independently selected from OR^3, SR^3, CN, $C\equiv CR^4$,
or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms;
15   R^3 is selected from C_{1-10} alkyl, C_{3-8} cycloalkyl, phenyl-C_{1-6} alkyl, phenyl or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms wherein the nitrogen containing heterocyclic ring is either unsubstituted or substituted with R^5 and R^6;
20   R^4 is C_{1-10} alkyl;

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R^5 and R^6 are each independently selected from CO_2R^4, COR^4 or C_{1-10} alkyl.

In one embodiment of this aspect of the invention is the compound of the formula
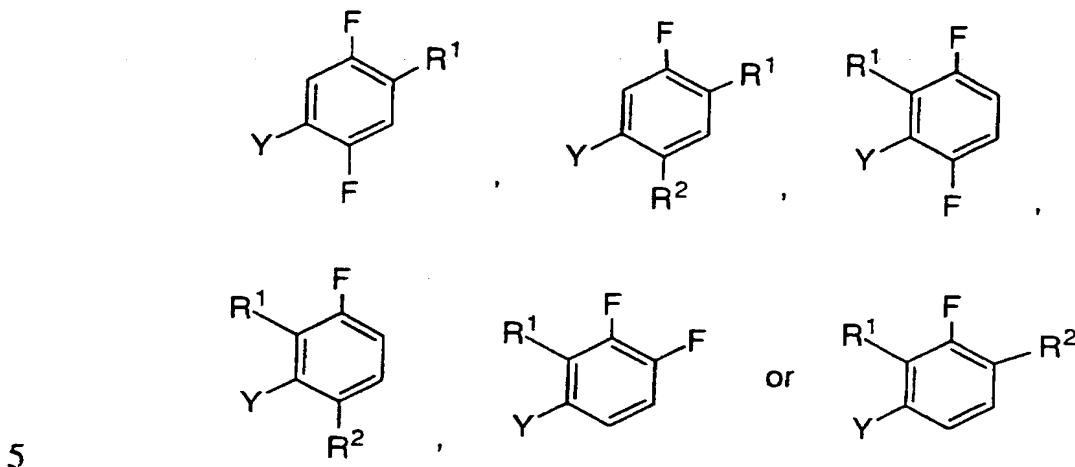
where all variables are as described above.

In a class of this aspect of the invention is the compound wherein

Y is selected from CN, CO_2H, CO_2CH_3, or $CO_2C(CH_3)_3$;

R^1 and R^2 are each independently selected from OR^3, SR^3, CN, $C \equiv CR^4$,

or a heterocyclic ring selected from
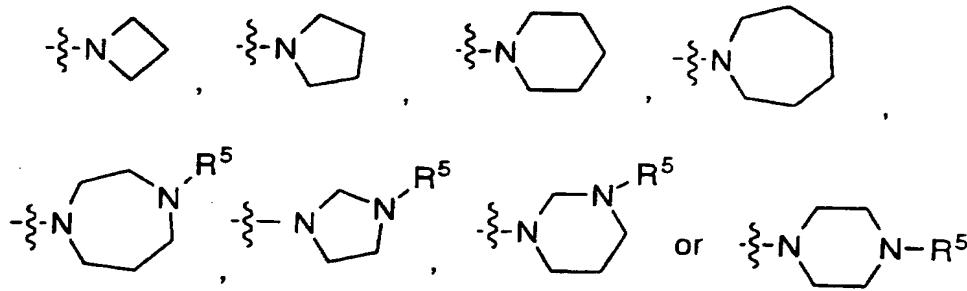
R^3 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, benzyl, phenyl or a heterocyclic ring selected from
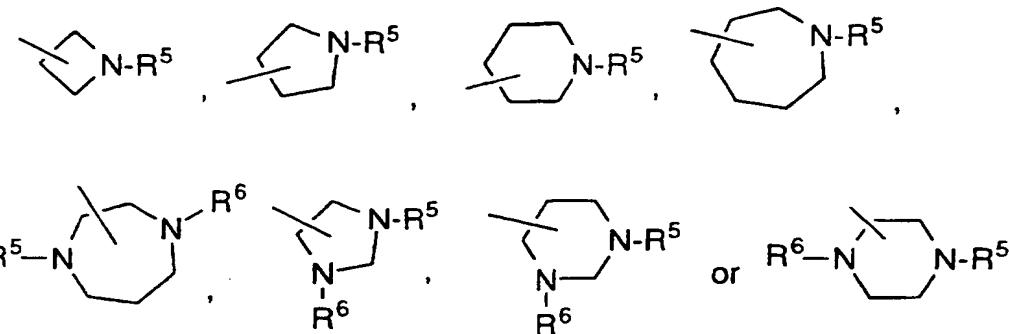
R^4 is C_{1-6} alkyl;

R^5 and R^6 are each independently selected from CO_2R^4. COR^4 or C_{1-6} alkyl.

5   In a subclass of this aspect of the invention is the compound of the formula

wherein R^1 is selected from

10   ; and
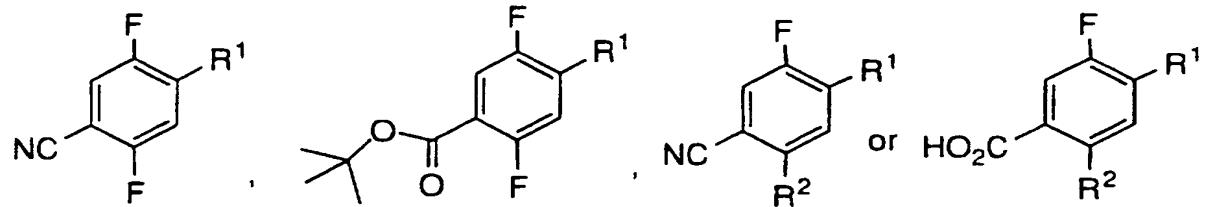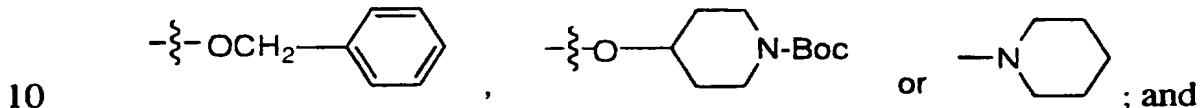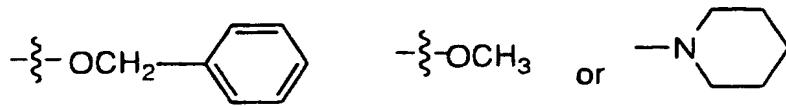
R^2 is selected from

An illustration of this aspect of the invention is the compound selected from
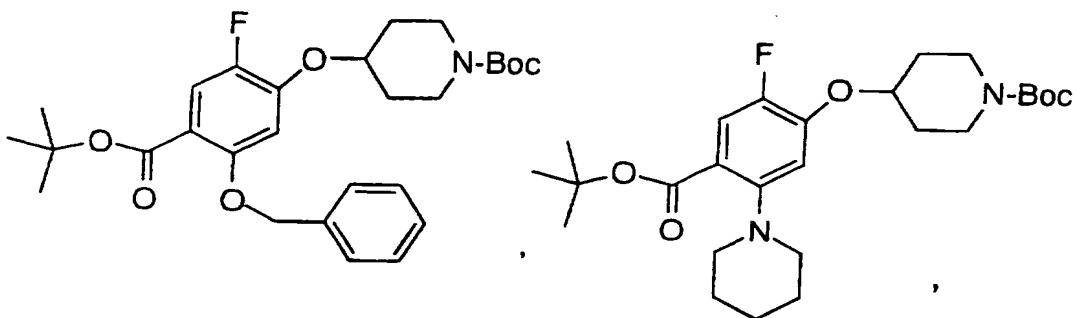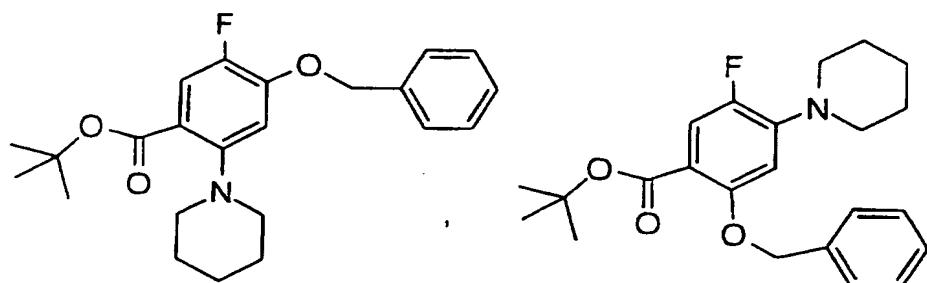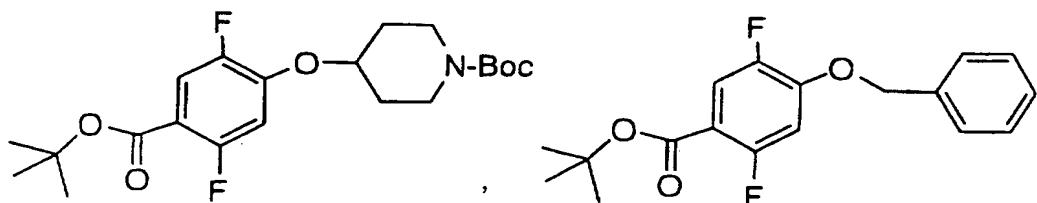
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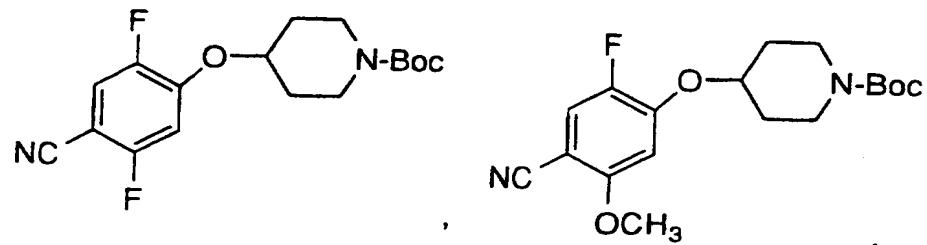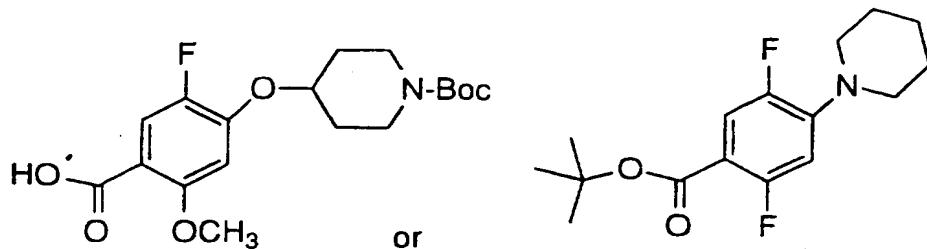
BRIEF DESCRIPTION OF THE DRAWINGS
Not Applicable

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DETAILED DESCRIPTION OF THE INVENTION

The instant invention provides a process for regioselective nucleophilic substitution of trifluorobenzoate and/or trifluoronitrile. In a preferred embodiment of the present invention, 2,4,5-trifluoro-

10   benzoate/trifluorobenzonitrile is regioselectively substituted at the 4-position by a nucleophile to afford the 2,5-difluorobenzoate/difluoro-benzonitrile in high yields. Preferably, the nucleophile is an oxygen nucleophile (e.g., alkoxide), a nitrogen heterocycle (e.g., piperidine), a sulfur nucleophile (e.g., thiol) or a carbon nucleophile (e.g., nitrile,

15   acetylene). Additionally, the resultant 2,5-difluorobenzoate/difluoro-benzonitrile can be subsequently substituted at the 2-position by a second nucleophile to afford the 5-fluorobenzoate/fluorobenzonitrile which is useful as an intermediate in the synthesis of fluorinated oxytocin antagonists, e.g., Compound A.

20   The nucleophilic substitution of trifluorobenzoate/trifluoro-benzonitrile to form the difluorobenzoate/ difluorobenzonitrile can be run at a temperature range of -78 to 5°C, preferably, -78 to -30°C, most preferably, about -65°C. Subsequent substitution of the difluoro-benzoate/difluorobenzonitrile with a nucleophile to form the

25   monofluorobenzoate/monofluorobenzonitrile can be run at a temperature range of -50 to 50°C, preferably, 20 to 25°C, most preferably, about 5°C.

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A variety of solvents can be utilized in the nucleophilic substitution reactions of the present invention. More specifically, the nucleophilic substitution reactions of the present invention can be run in a solvent selected from a hydrocarbon solvent (e.g., hexane,
5   cyclohexane) an aromatic solvent (e.g., toluene, benzene) or an oxygenated organic solvent (e.g., DMF, NMP, an ether). Examples of ethers which are suitable for use in the present invention include, but are not limited to, diethyl ether, tert-butyl methyl ether, and tetrahydrofuran. Preferably, an oxygenated organic solvent is utilized.
10 Most preferably, the reaction is run using THF, DMF or NMP as the solvent.

Abbreviations used in the instant specification are as follows:

AcOH or HOAc	=	acetic acid
Bn	=	benzyl
Boc or BOC	=	tert-butyloxycarbonyl
DCM	=	dichloromethane
DEAD	=	diethyl azodicarboxylate
DIEA	=	diisopropylethylamine
DMF	=	N, N-dimethylformamide
DMSO	=	dimethylsulfoxide
EDC	=	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	=	ethyl
EtOAc	=	ethyl acetate
EtOH	=	ethanol
eq.	=	equivalent
FAB MS	=	fast atom bombardment mass spectroscopy
Me	=	methyl
MeOH	=	methanol
MTBE	=	tert-butyl methyl ether
NMP	=	1-methyl-2-pyrrolidinone
Ph	=	phenyl
r.t.	=	room temperature
THF	=	tetrahydrofuran

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The compounds of the present invention, may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. Therefore, where a compound is chiral, the

5   separate enantiomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers. Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention.

The term "preterm labor" shall mean expulsion from the

10   uterus of a viable infant before the normal end of gestation, or more particularly, onset of labor with effacement and dilation of the cervix before the 37th week of gestation. It may or may not be associated with vaginal bleeding or rupture of the membranes.

The term "dysmenorrhea" shall mean painful menstruation.

15   The term "cesarean delivery" shall mean incision through the abdominal and uterine walls for delivery of a fetus.

The term "alkyl," as used herein, includes both straight and branched chain alkanes of the number of carbon atoms specified (e.g., C_{1-8} alkyl), or any number within this range (i.e., methyl, ethyl,

20   1-propyl, 2-propyl, n-butyl, s-butyl, t-butyl, etc.).

The term "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

The term "alkoxy," as used herein, refers to straight or

25   branched chain alkoxides of the number of carbon atoms specified (e.g., C_{1-5} alkoxy), or any number within this range (i.e., methoxy, ethoxy, etc.).

The term "phenyl-C_{1-6} alkyl" refers to a phenyl ring attached to a C_{1-6} alkyl group, e.g., benzyl, phenylethyl, phenylpropyl,

30   etc.

As used herein, the term "halogen" shall include, iodine, bromine, chlorine and fluorine.

The term "nitrogen heterocycle," as used herein, represents an unsubstituted or substituted stable 4- to 7-membered monocyclic

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saturated ring system which consists of carbon atoms and from one to two nitrogen heteroatoms; the heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such nitrogen heterocycles include, but is not
5   limited to, piperidinyl, piperazinyl, azepinyl, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl.

The term "oxygen nucleophile," as used herein, refers to an electron pair donor resided on an oxygen atom.

The term "sulfur nucleophile," as used herein, refers to an
10   electron pair donor resided on a sulfur atom.

The term "carbon nucleophile," as used herein, refers to an electron pair donor resided on an carbon atom.

The following examples are provided to further define the invention without, however, limiting the invention to the particulars of
15   these examples. For the compounds of Examples 1-14, which follow, ^{1}H NMR spectra were measured at 300 MHz on a Bruker AM-300 instrument, and ^{13}C NMR spectra were run at 75.5 MHz on the same instrument. ^{1}H and ^{13}C NMR spectras for the compounds of Examples 1-14 were consistent with structures.

20

EXAMPLE 1

Synthesis of Difluoroester 9 from Trifluoroester 8
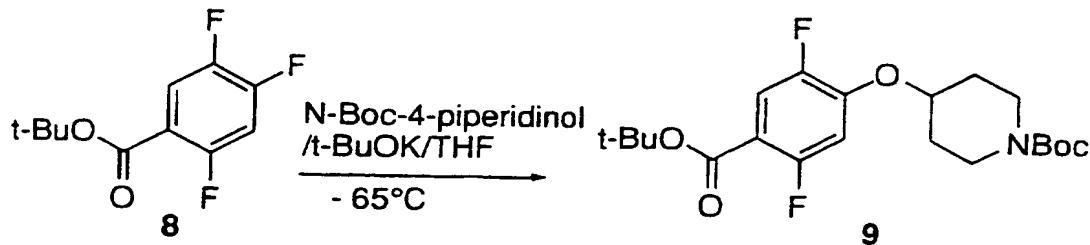
25   To a solution of N-Boc-4-piperidinol (1.95 g, 9.68 mmol) in THF (5.0 ml) was added a solution of t-BuOK in THF (Aldrich, 1.0 M, 10.6 ml) at 0°C and the resulting reaction mixture was stirred for 0.5 h at that temperature. The reaction mixture was slowly cannulated to a cold solution of trifluoroester 8 (2.05 g, 8.80 mmol) in THF (5.0

- 15 -

ml) at -65°C and was then aged at -30°C for 1.5 h. The reaction was
quenched with water (5.0 ml) at -30°C and then extracted with MTBE
(150 ml). The organic layer was washed with water (30 ml), then brine
(30.0 ml) and dried over MgSO4. Evaporation of the solvents gave an
oily residue. Chromatography of the residue on silica gel (eluted with
5% ethyl acetate/hexane) provided 2.31 g of the desired product **9**
(63.6% yield).

EXAMPLE 2

Synthesis of Monofluoroacid 5
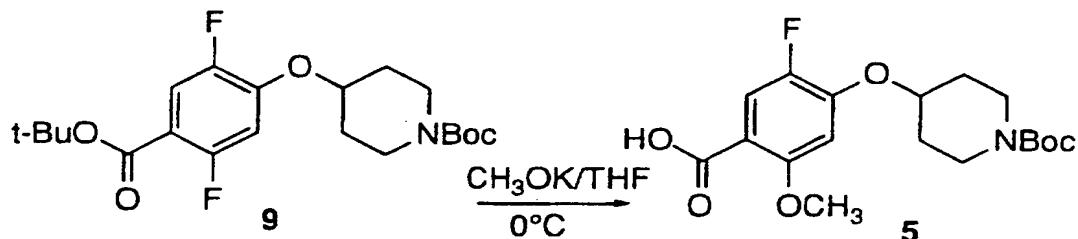
To a solution of t-BuOK in THF (1.0 M, 2.0 ml) was added
MeOH (0.081 ml, 2.0 mmol) at -4°C and the resulting solution was
stirred for 0.5 h. A THF solution of **9** (165 mg, 0.40 mmol) was
introduced at -4°C and the reaction mixture was stirred at 0°C for 1.0 h.
The reaction mixture was allowed to warm to 25°C and stirred for 6 h.
The reaction mixture was diluted with MTBE (25 ml) and water (25 ml)
at 25°C. The aqueous layer was separated and then neutralized with 2 N
HCl to pH = 1. The neutralized aqueous layer was extracted with
CH2Cl2 (25 ml x 2). The combined organic layers were washed with
water (25 ml) and dried over MgSO4. Evaporation of the solvent gave
the solid acid **5**.

EXAMPLE 3

Synthesis of Difluoronitrile 12 from Trifluoronitrile 11
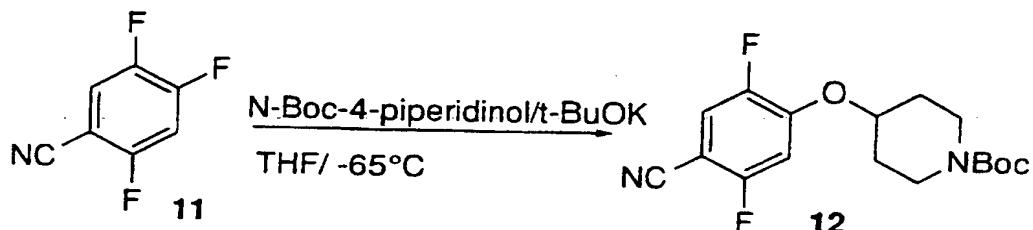
A t-BuOK solution (1.0 M, 5.0 ml) was slowly added to a solution of N-Boc-4-piperidinol (1.0 g, 4.97 mmol) in THF (3.0 ml) at 5°C and the resulting mixture stirred for 0.5 h. The mixture was then transferred to a cold solution of trifluoronitrile 11 (Aldrich, 0.569 ml, 4.97 mmol) in THF (3.0 ml) at -65°C. The reaction mixture was stirred at -65°C for 3.0 h and then allowed to warm to 25°C over 1.0 h. The reaction mixture was quenched with water (25 ml) and was diluted with MTBE (100 ml). The organic layer was separated and washed with water (35 ml), brine (35 ml), and dried over MgSO4. Evaporation of the solvent under vacuum provided 1.65 g of a white solid 12 (99% yield).

EXAMPLE 4

Synthesis of Monofluoronitrile 13 from Difluoronitrile 12
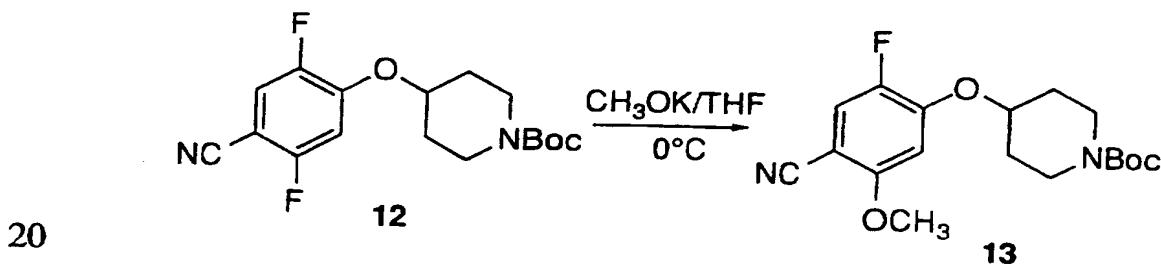
MeOH (0.151 ml, 3.73 mmol) was added to a solution of
t-BuOK in THF (1.0 M, 3.73 ml) at 5°C resulting in a light suspension
which was stirred for 0.5 h at 5°C. The light suspension was cannulated
into a cold solution of difluoronitrile **12** (0.84 g, 2.485 mmol) in THF

5   (3.0 ml) at -50°C and then aged for 1.0 h at -50°C. The reaction
mixture was warmed to 5°C over 0.5 h and stirred at 5°C for 2 h after
which the reaction was quenched with water (15 ml). The reaction
mixture was diluted with MTBE (100 ml), and the organic layer was
washed with water (35 ml), then brine (35 ml). After drying over

10   MgSO4, the organic layer was evaporated to dryness to provide a waxy
solid of monofluoronitrile **13** (0.83 g, 95% yield).

EXAMPLE 5

15   ### Synthesis of Monofluoroacid 5 from Monofluoronitrile 13
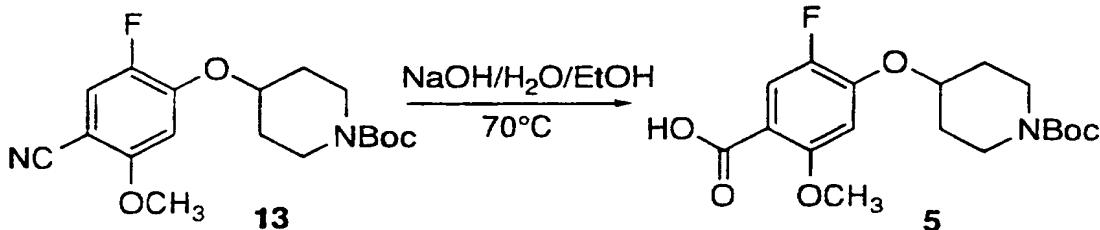
A NaOH solution (3.0 ml, 50 wt %) was added to a solution
of **13** (0.416 g, 1.19 mmol) in EtOH (3.0 ml), followed by addition of
water (3.0 ml) at 25°C. The resulting slurry was heated to 70°C for 16

20   h and then cooled to 5°C. Conc. HCl was added at 5°C to adjust the pH
to 1, and the mixture was then extracted with ethyl acetate (100 ml).
The organic layer was separated and washed with water (25 ml), brine
(25 ml) and dried over MgSO4. Evaporation of the solvent gave the
acid **5** as a white solid (0.40 g, 90% yield).

25

EXAMPLE 6

Synthesis of Monofluoroester 14 from Difluoroester 9

5   9
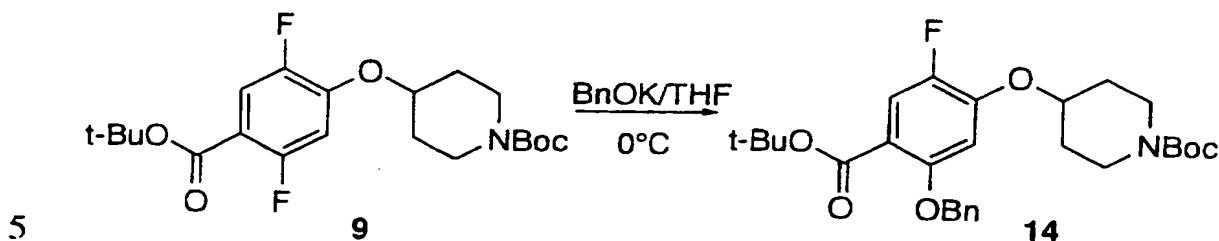
A solution of t-BuOK in THF (1.0 M, 0.55 ml) was added
to a solution of benzyl alcohol (0.057 ml, 0.55 mmol) in THF (2.0 ml)
at 5°C and the resulting mixture stirred at 5°C for 0.5 h. The
10   difluoroester 9 (206 mg, 0.5 mmol) was introduced as a solid at 5°C and
the reaction was stirred at 5°C for 4.5 h. The reaction was warmed to
25°C and stirred for an additional 1.5 h, then quenched with water (5.0
ml) and extracted with MTBE (50 ml). The organic layer was washed
with water (15 ml), brine (15 ml) and dried over MgSO4. Evaporation
15   of the solvent afforded the desired product 14.

EXAMPLE 7

Synthesis of Monofluoroester 15 from Difluoroester 9
20
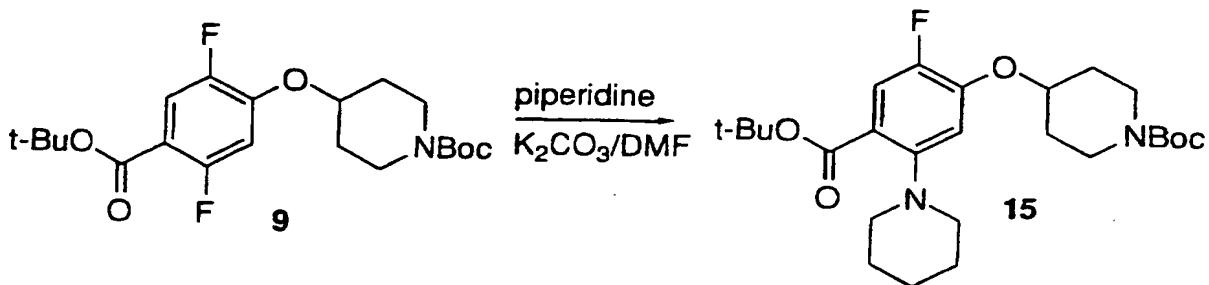
The starting material **9** (191 mg, 0.46 mmol), piperidine (0.0686 ml, 0.695 mmol) and potassium carbonate (128 mg, 0.928 mmol) were mixed together in DMF (5.0 ml) at 25°C. The slurry was stirred and heated to 110°C for 12 h. After cooling to 25°C, the

5   reaction mixture was diluted with water (15 ml) and extracted with MTBE (100 ml). The organic layer was separated and washed with water (25 ml x 2), sat. NaHCO₃ (20 ml) and brine (20 ml).
The organic layer was dried over MgSO₄ and evaporated to dryness. Chromatography of the residue on silica gel and elution with 15% ethyl

10   acetate/hexane provided **15** in 75% yield (160 mg).


EXAMPLE 8

Synthesis of Difluoroesters **16a** and **16b** from Trifluoroester **8**

15
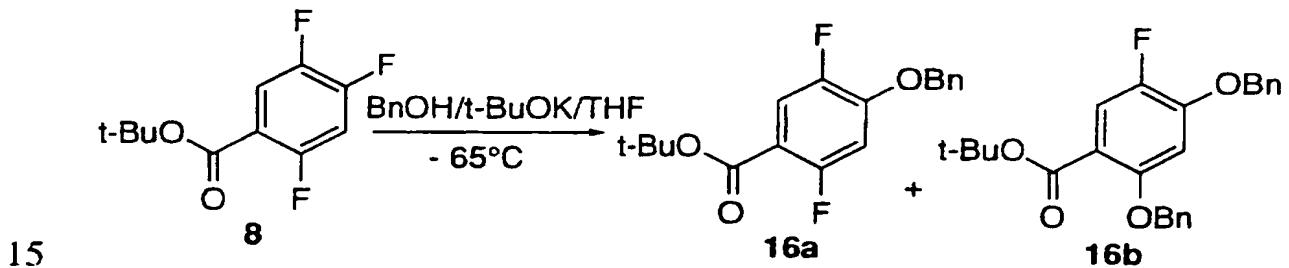
A solution of t-BuOK in THF (1.0 M, 1.06 ml) was added to a solution of benzyl alcohol (0.11 ml, 1.06 mmol) in THF (2.0 ml) at 5°C and the resulting mixture stirred at 5°C for 0.5 h. A solution of **8**

20   (205.4 mg, 0.88 mmol) in THF (2.0 ml) was introduced slowly at 5°C and kept at 5°C for 3.5 h. The reaction was warmed to 25°C for 0.5 h, and then the reaction was quenched with water and diluted with MTBE (100 ml). The organic layer was separated and washed with water (25 ml) and brine (25 ml), followed by drying over MgSO₄. Evaporation

25   of the solvent gave a residue which was chromatographed on silica gel. Elution with 5% ethyl acetate/hexane gave a first fraction containing difluoroester **16a** (114 mg, 40.5% yield) and a second fraction containing monofluoroester **16b** (107 mg, 29.8% yield).

EXAMPLE 9

Synthesis of Monofluoroester **17** from Difluoroester **16a**
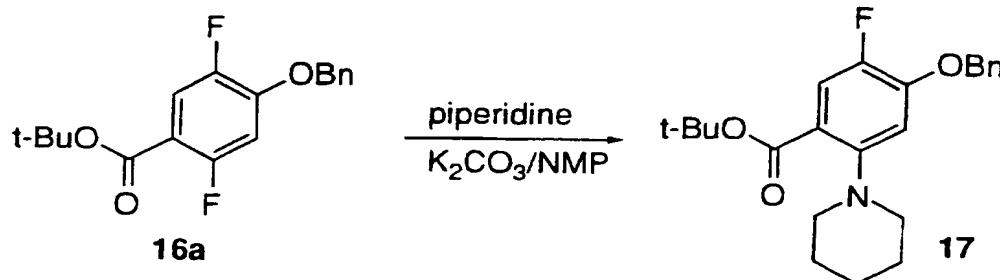
5   Piperidine (0.077 ml, 0.78 mmol) was added to a solution of difluoroester **16a** (100 mg, 0.31 mmol) in THF (2.0 ml) at 25°C, followed by addition of K_2CO_3 (86 mg, 0.62 mmol). The resulting suspension was stirred at 25°C for 2.0 h and then heated to reflux for 2.0 h. To this slurry was added NMP (2.0 ml) and refluxing continued
10   for 12 h. The reaction mixture was diluted with water (10 ml) and extracted with MTBE (100 ml). The organic layer was separated and washed with water (25 ml x 2), sat. $NaHCO_3$ (25 ml) and brine (25 ml). After drying over $MgSO_4$, the solvent was removed under vacuum to give the product **17**.

15

EXAMPLE 10

Synthesis of Difluoroester **18** from Trifluoroester **8**
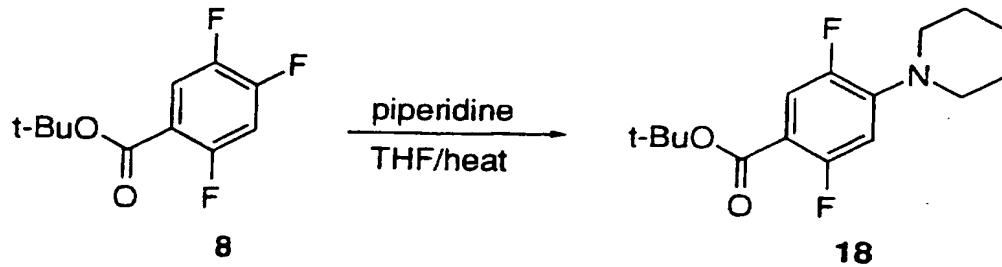
Piperidine (0.80 ml, 8.09 mmol) was added to a solution of trifluoroester **8** (0.84 g, 3.61 mmol) in THF (5.0 ml) at 25°C and the reaction mixture stirred for 1.0 h. The mixture was heated to reflux for 2 h, and then cooled to 25°C. The reaction mixture was diluted with
5   water (35 ml) and extracted with MTBE (150 ml). The organic layer was washed with sat. NaHCO3 (35 ml), brine (35 ml) and dried over MgSO4. Evaporation of the solvent gave the desired product **18** as an oil (1.04 g, 96.7% yield).

10   EXAMPLE 11

Synthesis of Monofluoroester **19** from Difluoroester **18**
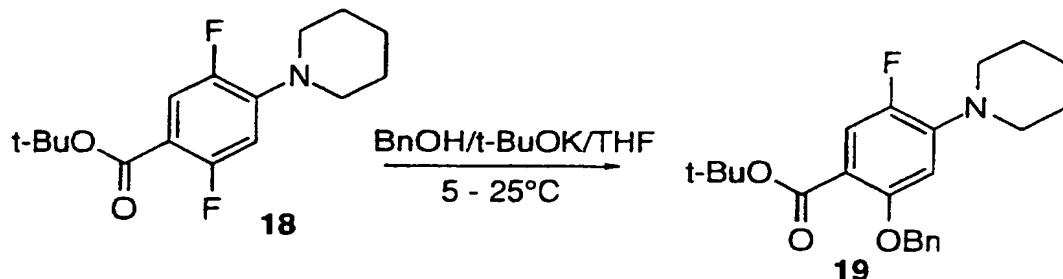
Benzyl alcohol (0.187 ml, 1.81 mmol) was added to a
15   solution of t-BuOK in THF (1.0 M, 1.81 ml) at 5°C and the resulting solution stirred for 0.5 h at that temperature. To this solution was added a solution of difluoroester **18** (538 mg, 1.81 mmol) in THF (2.0 ml) at 5°C over 10 min. The resulting solution was kept at 5°C for 1.5 h, then warmed to 25°C, and stirring continued for 2.0 h. The reaction
20   was quenched with water (5.0 ml) at 25°C and extracted with MTBE (150 ml). The organic layer was washed with water (25 ml) and brine (25 ml). After drying over MgSO4, the solvent was evaporated to give a residue which was chromatographed on silica gel and eluted with 10% ethyl acetate/hexane. Concentration of the appropriate fractions gave
25   the desired product **19** which was obtained as an oil (0.5 g, 70.4% yield).

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EXAMPLE 12

Synthesis of Difluoronitrile 21 from Trifluoronitrile 20
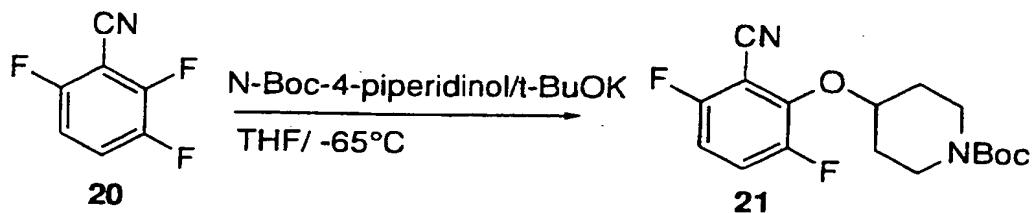
5   A solution of t-BuOK in THF (1.0 M, 3.18 ml) was added to a solution of N-Boc-4-piperidinol (0.64 g, 3.18 mmol) in THF (2.0 ml) at 5°C and the resulting solution stirred for 0.5 h at 5°C. The resulting solution was then slowly cannulated to a solution of trifluoronitrile 20 (Aldrich, 0.364 ml, 3.18 mmol) in THF (2.0 ml) at 10   -65°C. The reaction was stirred at -65°C for 3.0 h. Water (5.0 ml) was added to quench the reaction at -65°C and then the mixture was warmed to 25°C and extracted with MTBE (150 ml). The organic layer was separated and washed with water (25 ml) and brine (25 ml). After drying over MgSO4, the solvent was removed under vacuum to provide 15   the product 21 as a white solid which was used, without further purification, in the next step.

EXAMPLE 13

20   ### Synthesis of Monofluoronitrile 22b from Difluoronitrile 21
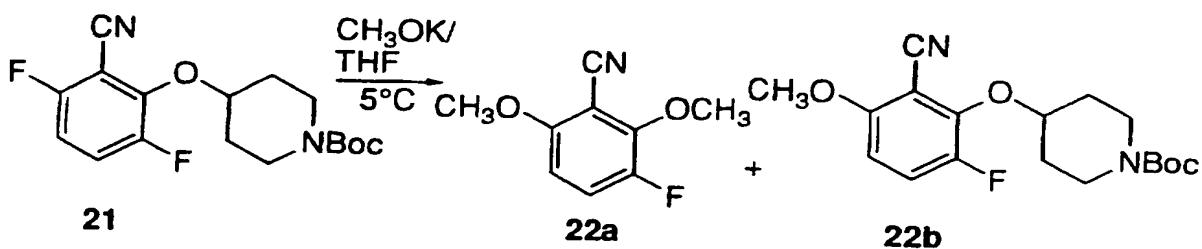
MeOH (0.258 ml, 6.36 mmol) was added to a solution of
t-BuOK in THF (1.0 M, 6.36 ml) at 5°C and the resulting light slurry
was stirred at 5°C for 0.5 h. The slurry was slowly transferred to a
cold solution of **21** (estimated: 3.18 mmol) in THF (4.0 ml) at -56°C

5   and stirred at that temperature for 2 h. The reaction was warmed to
5°C and kept at that temperature for 4 h. The reaction was quenched
with water (5.0 ml) at 5°C and extracted with MTBE (150 ml). The
organic layer was washed with water (25 ml), brine (25 ml) and dried
over MgSO4. Evaporation of the solvent afforded a residue which was

10   chromatographed on silica gel. Elution with 15% ethyl acetate/hexane
gave a first fraction containing product **22a** and a second fraction
containing the desired product **22b**.

EXAMPLE 14

15

Synthesis of Difluoronitrile **24** from Trifluoronitrile **23**
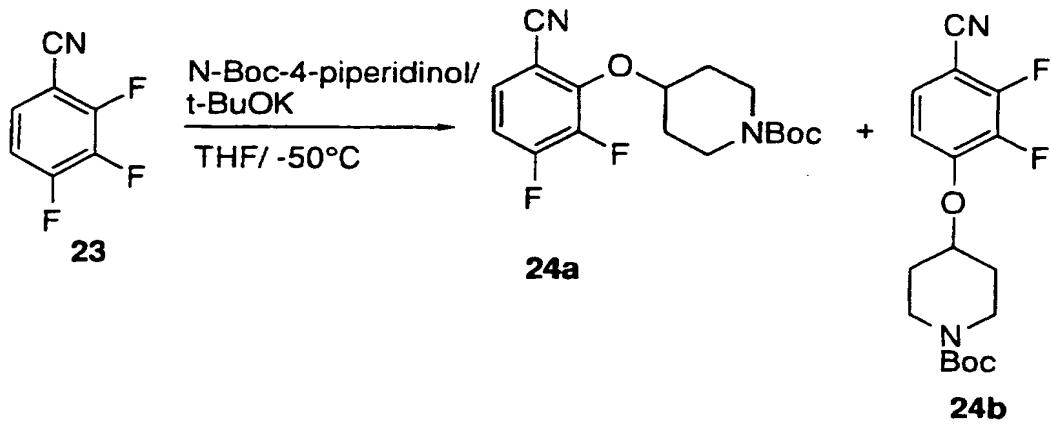

A solution of t-BuOK in THF (1.0 M, 6.30 ml) was added
to a solution of N-Boc-4-piperidinol (1.23 g, 6.1 mmol) in THF (4.0

20   ml) at -40°C and the resulting solution stirred for 0.5 h at -40°C. The
resulting solution was slowly cannulated to a solution of trifluoronitrile
23 (Aldrich, 0.364 ml, 3.18 mmol) in THF (4.0 ml) at -50°C. The
reaction was stirred at -50°C for 0.5 h. Water (5.0 ml) was added to
quench the reaction at -50°C and the reaction was then warmed to 25°C.

25   The reaction mixture was extracted with MTBE (150 ml) and the

- 24 -

organic layer was separated, washed with water (25 ml) and dried over MgSO4. The organic layer was evaporated to give a residue which was chromatographed on silica gel. Elution with 15% ethyl acetate/hexane gave a first fraction containing product **24a** (64%) and a second fraction containing product **24b** (14%).

Compound **A** was prepared from Monofluoroacid **5** according to Examples 15 to 17 which follow. For examples 15-17 which follow, ^{1}H NMR spectra were measured at 300 MHz on a Varian XL-300, at 400 MHz on a Varian XL-400, and at 360 MHz on a Nicolet NT-360 using (CH3)4Si as an internal standard and Fast atom bombardment mass spectra (FAB MS) were obtained on a VG-ZAB-HF spectrometer. All NMRs for the compounds of Examples 15-17 which follow were consistent with structures.

EXAMPLE 15

1-(1-(4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one
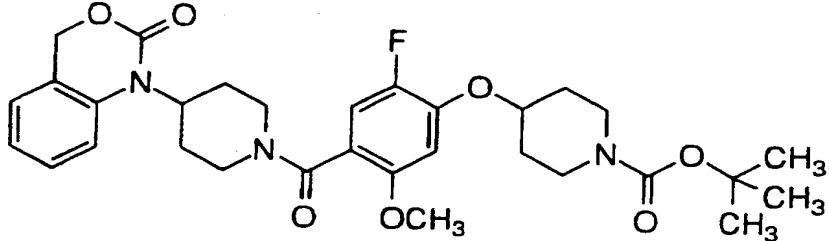
Step 1: 1-t-Butyloxycarbonyl-4-piperidinone (20 g, 0.10 mol), 2-aminobenzyl alcohol (13 g, 0.11 mol), and acetic acid (14 mL, 0.22 mol) were dissolved in dry toluene (500 mL). The solution was refluxed under inert atmosphere for 3 h with azeotropic removal of water. The solution was cooled to ambient temperature and concentrated under reduced pressure to one half of the original volume. To the solution was added NaBH3CN (20 g, 0.32 mol) and dry THF (300 mL). Acetic acid (10 mL, 0.15 mmol) was added dropwise over a period of about 1 h. The reaction was stirred at ambient temperature for 24 h.

The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (750 mL). The EtOAc layer was washed with saturated aqueous NaHCO3 (3x 500 mL) and brine (250 mL).

5   The EtOAc layer was dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography, using a gradient elution of 15-30% EtOAc-hexanes. 1-t-Butyloxycarbonyl-4-((2-hydroxymethyl)-phenylamino)piperidine was obtained as a gum (TLC: R_f = 0.30 (30:70 EtOAc:hexanes); HPLC(method A) retention time = 8.89 min).

10   Step 2: 1-t-Butyloxycarbonyl-4-((2-hydroxymethyl)-phenylamino)piperidine (24 g, 78 mmol) from Step 1 above was dissolved in dry THF (250 mL) and cooled to 0°C under an atmosphere of nitrogen. To the solution was added DIEA (41 mL, 0.24 mol) and triphosgene (8.54 g, 28.8 mmol). The reaction was stirred at 0°C for 1h, and then at

15   ambient temperature for 24 h. Ether (250 mL) was added, the mixture was cooled to 0°C and then filtered to remove the hydrochloride salt of DIEA. The filtrate solvents were removed under reduced pressure and the residue was dissolved in EtOAc (750 mL). The EtOAc solution was washed with 5% aqueous citric acid (2x 500 mL), water (250 mL), and

20   saturated aqueous NaHCO3 (2x 500 mL). The EtOAc layer was dried (MgSO4), filtered, and the solvent was removed under reduced pressure. The residue was boiled in ether (ca. 200 mL) until the solid had dissolved. Cooling overnight gave 1-(N-t-butyloxycarbonyl-4-piperidinyl)-4H-3,1-benzoxazin-2(1H)-one as off-white crystals, mp 143-145°C (TLC: R_f =

25   0.28 (30:70 EtOAc:hexanes); HPLC(method A) retention time = 8.77 min; FAB MS: m/z 333 (M^+ + H)).

                Step 3: A stirred solution of 1-(N-t-butyloxycarbonyl-4-piperidinyl)-4H-3,1-benzoxazin-2(1H)-one (19 g, 57 mmol) from Step 2 above in EtOAc (500 mL) was cooled to 0°C. HCl gas was bubbled

30   through the solution for 30 min. Stirring was continued at 0°C for 1 h, during which time a precipitate had formed, and the reaction was warmed to ambient temperature for 1 h. The stirred suspension was cooled to 0°C and cold ether (250 mL) was added. The precipitate was collected by filtration and washed with ether. The solid was dried under

- 26 -

reduced pressure for 18 h, giving 1-(4-piperidinyl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride as a white amorphous solid (TLC: $R_f = 0.29$ (90:10:1 CH_2Cl_2:MeOH:NH_4OH); HPLC(method A) retention time = 3.88 min; FAB MS: m/z 233 ($M^+ + H$)).

5   Step 4: To a solution of the hydrochloride salt of 1-(4-piperidinyl)-4(H)-3,1-benzoxazin-2(1H)-one (150 mg, 0.56 mmol) from Step 3 above in DMF (5 mL) was added 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoic acid, 5 (206 mg, 0.56 mmol), HOBT (92 mg, 0.60 mmol), and EDC (140 mg, 0.73 mmol).
10   To the stirred solution was added DIEA (0.19 mL, 1.1 mmol) until the reaction was pH 7 as judged by spotting an aliquot on wetted E. Merck "colorpHast" pH 1-14 indicator strips. The reaction was stirred at ambient temperature for 18 h and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and
15   washed with 5% aqueous citric acid (25 mL), water (25 mL), and saturated aqueous $NaHCO_3$ (25 mL). The EtOAc layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 1-3% MeOH-$CHCl_3$. The
20   title compound, 1-(1-(4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained as an amorphous solid.

Analysis   calculated for $C_{31}H_{38}FN_3O_7$, 0.2 EtOAc, 0.25 H_2O
              C, 63.04; H, 6.67; N, 6.94
25   Found: C, 63.06; H, 6.56; N, 6.93
TLC: $R_f = 0.17$ (4:1 EtOAc:hexanes)
HPLC (method A) retention time = 9.8 min
FAB MS m/z 584 ($M^+ + H$)

EXAMPLE 16

1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one
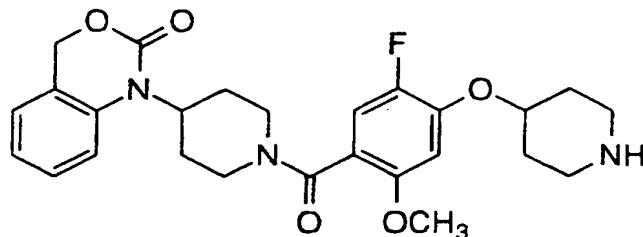

5

1-(1-(4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one from Example 15 was converted to the title compound using a procedure analogous to that given in Step 3 of Example 15. The
10 hydrochloride salt of 1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained as an amorphous solid.

Analysis   calculated for $C_{26}H_{30}FN_3O_5$, 2.0 HCl, 0.15 EtOAc
            C, 56.08; H, 5.87; N, 7.38
15 Found: C, 56.02; H, 5.94; N, 7.37
TLC: R_f = 0.12 (96:4:0.4 CH_2Cl_2:MeOH:NH_4OH)
HPLC(method A) retention time = 6.2 min
FAB MS m/z 484 (M^+ + H)

20   EXAMPLE 17

1-(1-(4-(N-acetyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one, Compound A

- 28 -
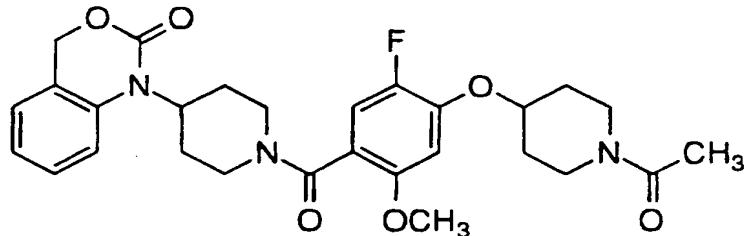
To a stirred solution of 1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one of Example 16 (200 mg, 0.41 mmol) in DCM (5 mL) at ambient temperature was added acetic anhydride (77 mg, 0.75 mmol) and DIEA
5   (0.17 mL, 1.0 mmol). The solution was stirred at ambient temperature for 24 h, diluted with DCM (20 mL), washed with saturated aqueous NaHCO3 (50 mL), dried (MgSO4), and filtered. The solvent was removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using a gradient elution
10   of 2-5% MeOH-DCM. 1-(1-(4-(N-acetyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained as an amorphous solid.

Analysis   calculated for $C_{28}H_{32}FN_3O_6$, 0.45 EtOAc, 0.65 H_2O
             C, 62.03; H, 6.45; N, 7.28
15   Found: C, 62.02; H, 6.22; N, 7.26
TLC: R_f = 0.33 (97:3 CH_2Cl_2:MeOH)
HPLC (method A) retention time = 7.4 min
FAB MS m/z 526 (M^+ + H)

20   While the foregoing specification teaches the principles of the present invention, with examples for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

WHAT IS CLAIMED IS:

1.   A compound of the formula

or
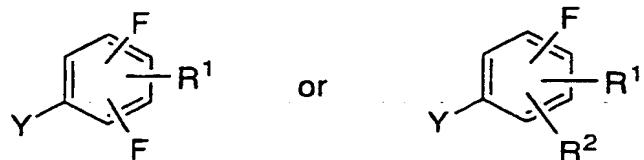
5   wherein Y is selected from CN, CO_2H or CO_2-C_{1-6} alkyl;
R^1 and R^2 are each independently selected from OR^3, SR^3, CN,
$C \equiv CR^4$,
or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic
ring containing one or two nitrogen atoms;
10   R^3 is selected from C_{1-10} alkyl, C_{3-8} cycloalkyl, phenyl-C_{1-6} alkyl,
phenyl or a 4, 5, 6 or 7-membered monocyclic nitrogen containing
heterocyclic ring containing one or two nitrogen atoms wherein the
nitrogen containing heterocyclic ring is either unsubstituted or
substituted with R^5 and R^6;
15   R^4 is C_{1-10} alkyl;
R^5 and R^6 are each independently selected from CO_2R^4, COR^4 or
C_{1-10} alkyl.

2.   The compound of Claim 1 of the formula

20
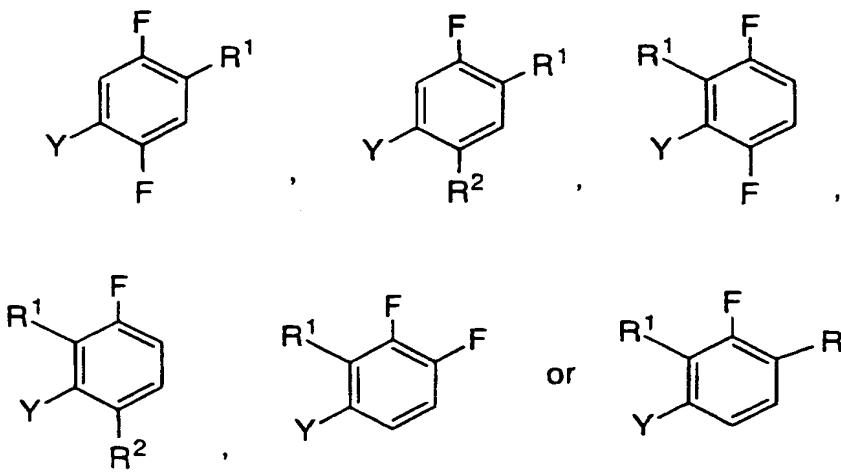
3.   The compound of Claim 2, wherein
Y is selected from CN, CO_2H, CO_2CH_3, or $CO_2C(CH_3)_3$;
R^1 and R^2 are each independently selected from OR^3, SR^3, CN,
$C\equiv CR^4$,

5   or a heterocyclic ring selected from
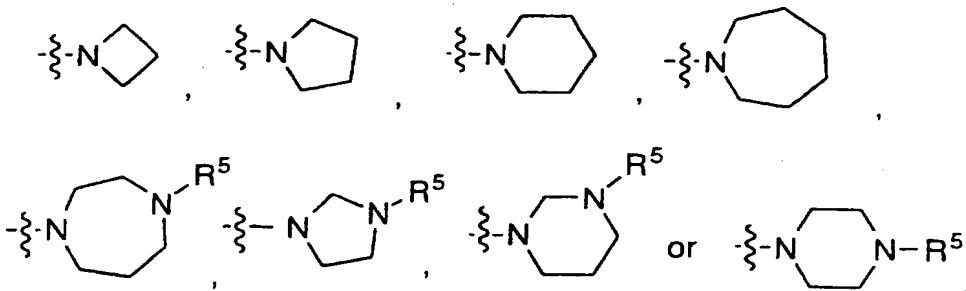
R^3 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, benzyl, phenyl or a
heterocyclic ring selected from
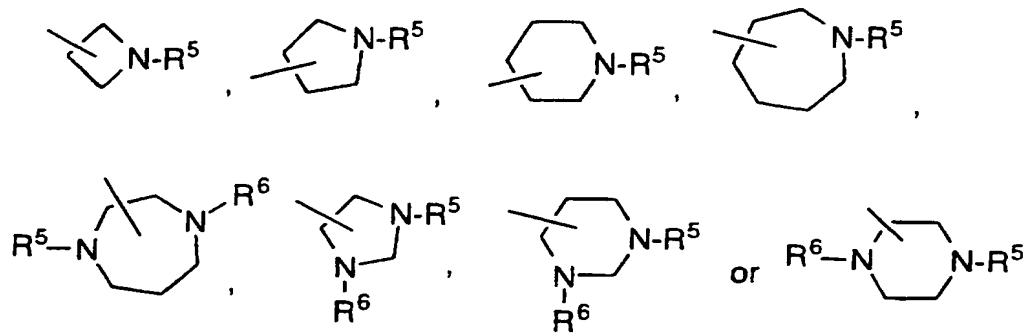
10   R^4 is C_{1-6} alkyl;
R^5 and R^6 are each independently selected from CO_2R^4, COR^4 or
C_{1-6} alkyl.

4.   The compound of Claim 3 of the formula

wherein R^1 is selected from


; and
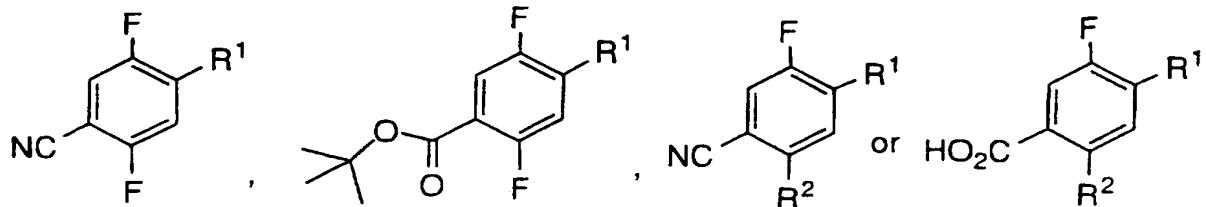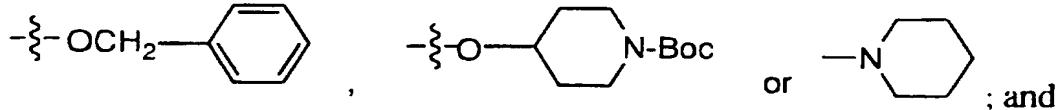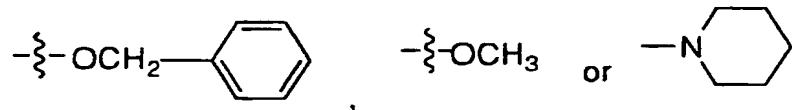
R^2 is selected from

5.   The compound of Claim 4, selected from


- 32 -
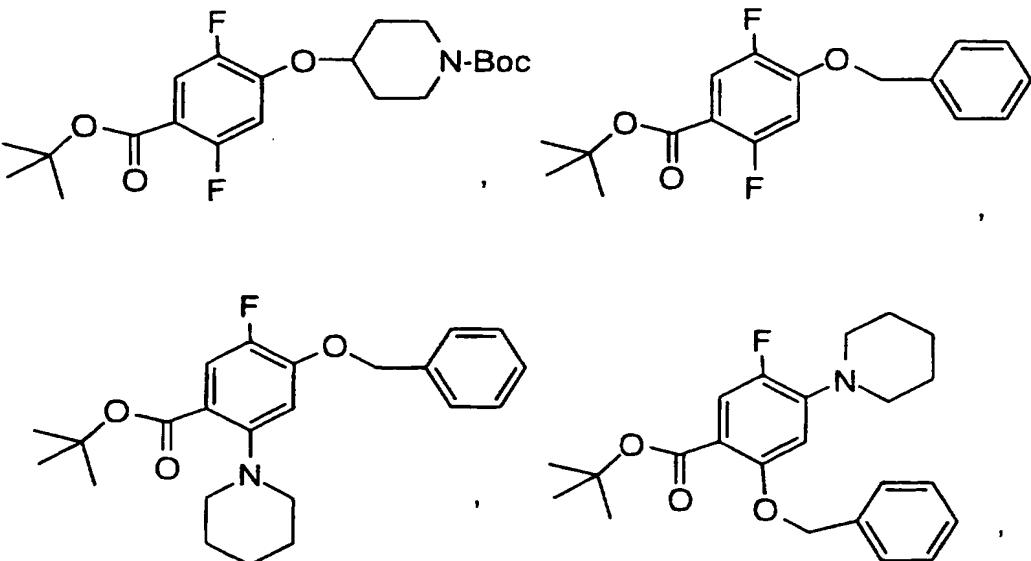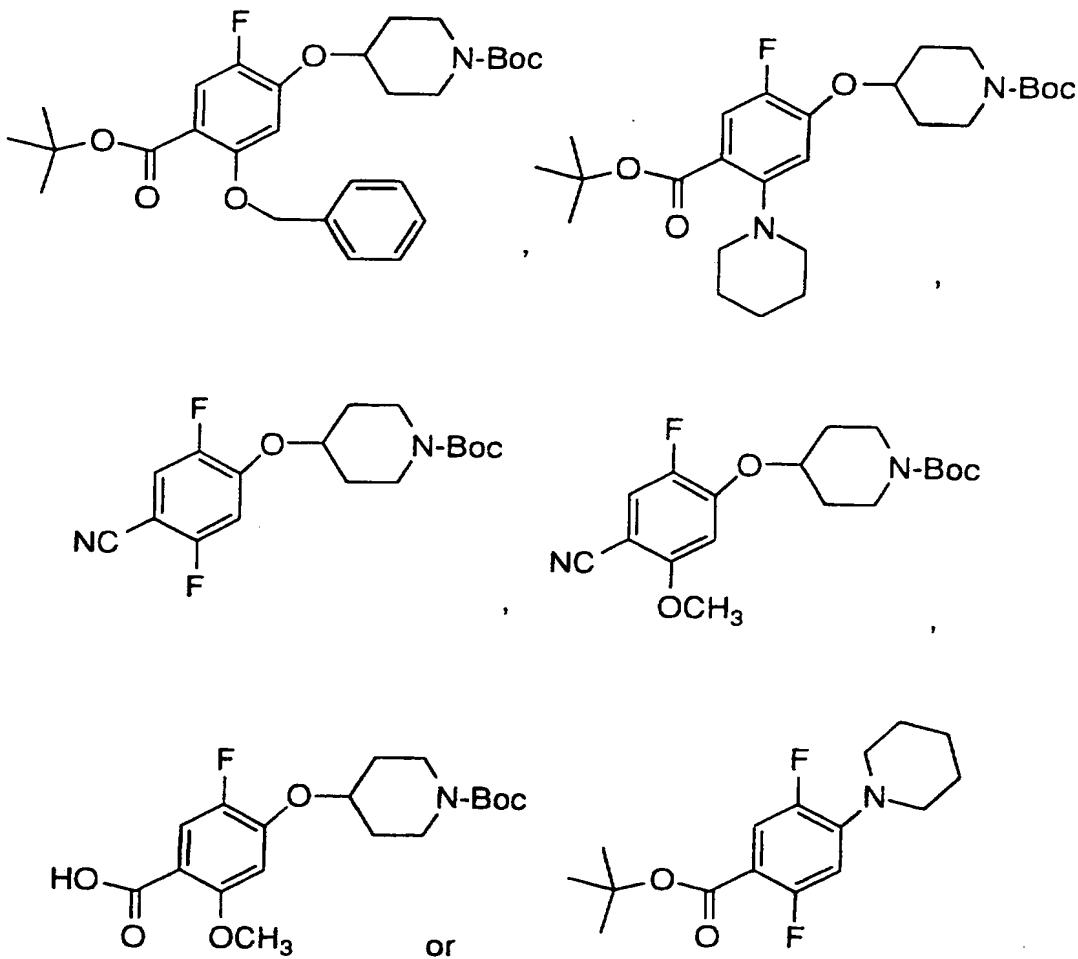
5   6.   A process for forming a difluoro compound I
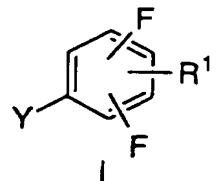
comprising reacting a trifluoro compound II
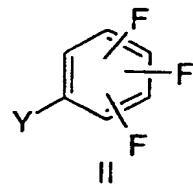
with a nucleophilic agent R^1 to obtain the difluoro compound I
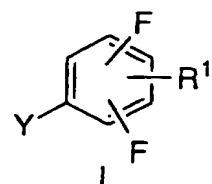
wherein Y is selected from CN or CO_2-C_{1-6} alkyl;

5   R^1 is selected from OR^3, SR^3, CN, $C\equiv CR^4$,

or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic ring containing one or two nitrogen atoms;

R^3 is selected from C_{1-10} alkyl, C_{3-8} cycloalkyl, phenyl-C_{1-6} alkyl, phenyl or a 4, 5, 6 or 7-membered monocyclic nitrogen containing

10   heterocyclic ring containing one or two nitrogen atoms wherein the nitrogen containing heterocyclic ring is either unsubstituted or substituted with R^5 and R^6;

R^4 is C_{1-10} alkyl; and

R^5 and R^6 are each independently selected from CO_2R^4, COR^4 or

15   C_{1-10} alkyl.

7.   The process of Claim 6, wherein the trifluoro compound is selected from

IIa   ,   IIb   or   IIc
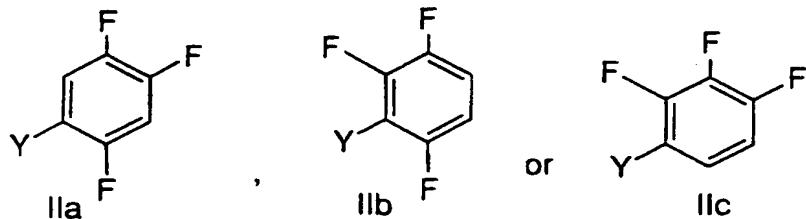
20   and the difluoro compound is selected from
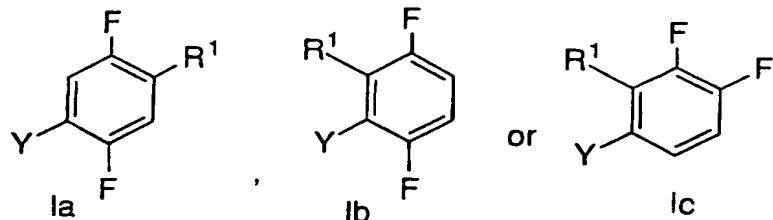
8.   The process of Claim 7, wherein the trifluoro compound is

5
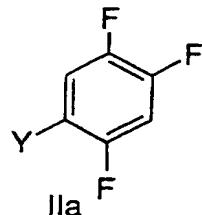
and the difluoro compound is
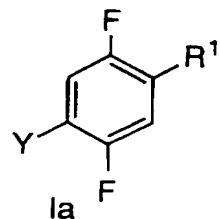
9.   The process of Claim 7, further comprising the step
10   of reacting the difluoro compound selected from
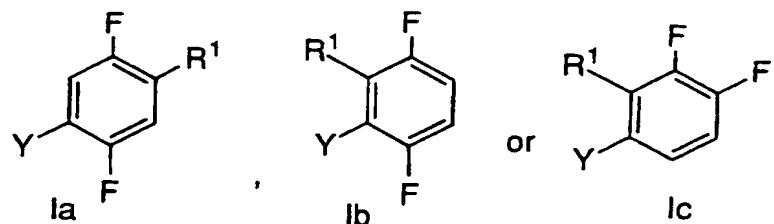
with a second nucleophilic agent R^2 to obtain a monofluoro compound selected from
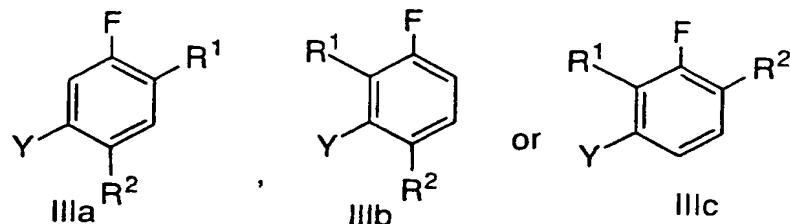
wherein R^2 is selected from OR^3, SR^3, CN, $C\equiv CR^4$,
or a 4, 5, 6 or 7-membered monocyclic nitrogen containing heterocyclic
ring containing one or two nitrogen atoms.

10. The process of Claim 9, wherein the difluoro
compound is
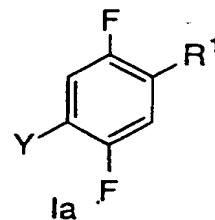
and the monofluoro compound is
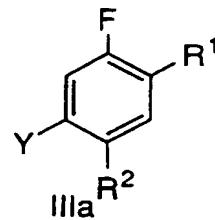
11. The process of Claim 6, wherein the reaction is run
at a temperature range of about -78°C to about 5°C.

12. The process of Claim 11, wherein the reaction is run
at a temperature range of about -78°C to about -30°C.

13. The process of Claim 12, wherein the reaction is run
at a temperature of about -65°C.

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14. The process of Claim 9, wherein the reaction of the difluoro compound with the second nucleophile is run at a temperature range of about -50°C to about 50°C.

5   15. The process of Claim 14, wherein the reaction of the difluoro compound with the second nucleophile is run at a temperature range of about -20°C to about 25°C.

16. The process of Claim 15, wherein the reaction of the
10   difluoro compound with the second nucleophile is run at a temperature of about 5°C.

17. The process of Claim 6, wherein the reaction is run in a solvent selected from a hydrocarbon solvent, an aromatic solvent or
15   an oxygenated organic solvent.

18. The process of Claim 17, wherein the solvent is an oxygenated organic solvent.

20   19. The process of Claim 18, wherein the solvent is selected from THF, DMF or NMP.

20. The process of Claim 9, wherein the reaction is run in a solvent selected from a hydrocarbon solvent, an aromatic solvent or
25   an oxygenated organic solvent.

21. The process of Claim 20, wherein the solvent is an oxygenated organic solvent.

30   22. The process of Claim 21, wherein the solvent is selected from THF, DMF or NMP.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/02877

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07C 255/33, 255/35, 255/49

US CL :558/415, 416, 419, 423

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 558/415, 416, 419, 423

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,332,851 A (KUMAI et al.) 26 July 1994, see entire document, especially column 2, lines 20-54.	1-22 (in part)
X	US 4,684,734 A (KAIEDA et al.) 04 August 1987, see entire document, especially columns 9 and 10.	1-22 (in part)

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
"O"	document referring to an oral disclosure, use, exhibition or other means	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 MAY 1997	11 JUL 1997

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer EBENEZER SACKEY
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/02877

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-22 (in part)

Remark on Protest   ☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1))(July 1992)*